Paper AR03

ADaM-Based Centralized Monitoring

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ABSTRACT

Efficient centralized monitoring during trial conduct relies on clinical data summaries, visualizations and the derivation of parameters or flags, which assists in the identification of issues. Analysis data (ADaM) likewise summarize and highlight aspects of data but is oftentimes solely designed with the clinical trial report in mind.

Basing the monitoring on ADaM datasets avoids any parallel developments and derivations. In addition, it enables the clinical team to operate on the same representation of data which eases communication greatly. However, this introduces additional constraints to ADaM programming.

This paper will be an overview of a solution, which uses Qlik Sense® as a data visualization tool on top of ADaM and a discussion of advantages and challenges of the approach.

INTRODUCTION

Often centralized monitoring (CM) is performed separately from ADaM dataset development. Part of the reason is the difference in timelines; whereas ADaM datasets are only required for the final reporting, centralized monitoring needs to start in early trial conduct.

However, the two do not need to be separate processes – in fact there may be gains to be made by basing the centralized monitoring on ADaM datasets.

OUR SOLUTION

Trial risks appropriate for ADaM-based centralized monitoring are identified as part of the risk management planning well in advance of study start. The risks are (re)phrased in terms of monitoring procedures and measures. Primarily measures which require derivation are defined to be in scope for ADaM-based CM.

Typically the relevant risks are associated with the trial endpoints or safety of the trial and in this sense often align very well with the production necessary for the clinical trial report (CTR).

Qlik Sense is used as a data visualization tool for monitoring. It is an intuitive interface to data which enables the setup of visualizations, tables and listings which the monitors can interact with directly to select e.g. populations of interest within the study. Data is cross-linked by specifying table keys, such as the unique subject ID which enables selection of data across ADaM domains.

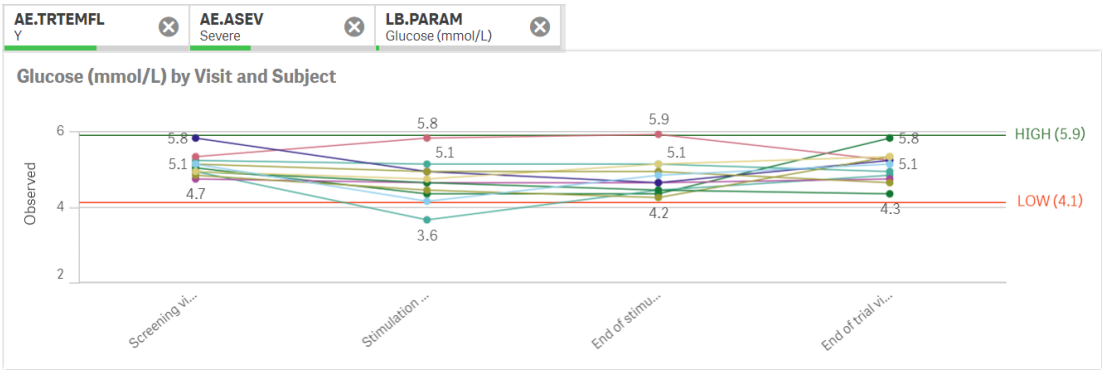


Figure 1: Glucose levels for subjects with severe, treatment emergent adverse events. The population and parameter are selected within the application and the visual dynamically updated. Labels for parameters and visits are carried forward from ADaM.

Moreover, once appropriately set up, Qlik Sense allows for breakdowns of data by groups of interest (e.g. by site, country, gender) to monitor trends and group differences and for management of monitoring comments and statuses on issues or other cases of interest.

With automated daily updates of study data, SDTM, ADaM and Qlik Sense visualizations the trial can be readily monitored and explored at any point of the trial.

INITIALIZATION AND TIMELINES

Introduction of ADaM-based centralized monitoring changes the trial programming timelines. Whereas traditional ADaM datasets need only be final prior to database lock, the data for centralized monitoring need to be available with first patient first visit (FPFV) – or latest when the data volume necessitates trends and summaries.

This means that part of the programming workload is shifted from the final to the early stages at the trial. Once appropriately factored into planning, however, this might result in a less intensive workload towards trial conclusion.

Several factors can ease the initial roll-out: reusability of code due to standardization, previous studies with similar data and the option of staged roll-outs due to the limited amount of data for endpoints available early in trial conduct. At Ferring the ADaM programming is often initiated on trial-specific test-SDTM data generated in large from eCRF metadata well in advance of FPFV – see reference [1].

DATA AND DERIVATIONS

The double usage of ADaM datasets means that some complications arise.

A frequently occurring case is the derivation of statuses during trial conduct to account for all subjects in the monitoring application. Specifically, as data is often not final, an ‘ongoing’ status may be required. This requires extra programming and care that all ‘ongoing’ statuses are implemented such that they do not remain at study finalization.

To mention a simple example, consider the screening status. If the trial has a prolonged screening phase, then a part of the subjects who has given informed consent may be undergoing screening. To have an overview of the trial population and for the purpose of forecasting, it may be relevant to know how many.

Lag between data points, such as a delay between entry of CRF pages due to site procedures, can also pose a challenge for the correct presentation of data. Did an expected event happen, is it delayed or non-occurring or was there a protocol deviation? And how big a delay makes it relevant for flagging to the monitor?

As data is not final, updates to the source data happen. This can cause statuses and outcomes to fluctuate – something which is an expected feature of live data. However, such changes may occur more frequently than towards trial completion and require more time invested in stakeholder management than is the case for traditional trial programming - especially if the case was of interest to the trial monitor.

Imputations of data for analysis purposes can likewise pose a challenge. In the monitoring application such imputations can give the faulty impression that more data, in form of e.g. subjects, assessments or events, is available in the trial than is actually the case. If for instance zero-counts are imputed for subjects without an assessment, where it was expected, then the number of subjects with the given parameter occurs larger than it actually is – which then can result in lower-than-expected mean counts.

Finally, as ADaM datasets have downstream dependence, the update of datasets requires some caution. No draft or faulty datasets used for monitoring should be left in production.

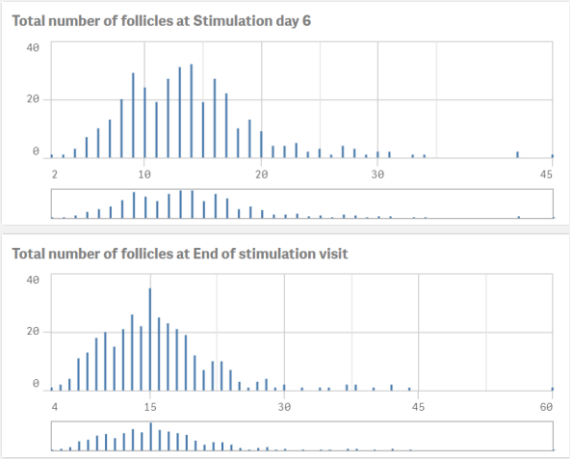
ADVANTAGES

The immediate advantage of the approach is to avoid double derivations of endpoints. This is not just an advantage in terms of workload but also ensures that only one interpretation of their definitions is implemented.

In the case ambiguities arise this means that the clinical trial team has to discuss and agree on the intended implementation. This discussion oftentimes proves fruitful, highlights additional nuances and perspectives and ultimately improves the quality of how endpoints are derived.

Additionally, it provides an additional review of data such that source data issues or issues in any of the endpoint derivations can be readily corrected.

Using the same data as a basis also means that it is easier for differing stakeholders to communicate. There are no slightly differing implementations, labels which have partial overlaps or differences in data structures which provide an obstacle for communication. Labels in tables, listings, figures and in the centralized monitoring application match each other – as displayed in figure 2.



Total number of follicles by visit and stratum - Full Analysis Set

	TREATMENT A		TREATMENT B	
Stratum	Median	[IQ-range]	Median	[IQ-range]
Visit: Stimulation day 6				
All observations	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]
Stratum A	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]
Stratum B	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]
Visit: End of stimulation visit				
All observations	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]
Stratum A	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]
Stratum B	XX.X	[XX.X; XX.X]	XX.X	[XX.X; XX.X]

[IQ-range] = Inter-quartile range

FEXXXXXX/ABC/XXXXXX/Report/01JAN1960-ANON/FOLLICLES_SUM.sas

Figure 2: Data display from Qlik Sense (left) and End-of-Text (right). In both cases labels are extracted from ADaM so parameters from PARAM and visits from AVISIT.

CONCLUSION

ADaM-based Centralized Monitoring aligns derivations and presentations of trial endpoints, facilitates common understanding of trial derivations and definitions in the trial team and increases quality of reported results.

It lessens the amount of parallel derivations necessary but comes at the cost of increased complexity of derivations and more time spent on discussions with stakeholders regarding definitions and implementations.

REFERENCES

[1]: Phuse Connect 2018, PP12: Need for Speed – Accelerating Centralised Monitoring, Parag Naithani & Pramod Chittam, Ferring Pharmaceuticals.

CONTACT INFORMATION

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